

**REMARKS**

Applicant respectfully requests reconsideration of this application in view of the foregoing amendments and the following remarks.

**A. Introductory Remarks**

It is acknowledged that the amendments are being made after a final rejection of the claims. Nevertheless, Applicant respectfully requests entry of the amendments because they place the application in condition for allowance or at least better condition for appeal, without requiring further searching or introducing new matter into the application.

Upon entry of the amendments, claims 41-44, 46-49 and 51 will be pending in the application. Claims 41, 46-47 and 51 are currently being amended. Support for the amendments to those claims exists at pages 10-13 of the specification. No claims are currently being added. Claims 45, 50 and 52-67 are currently being canceled without prejudice or disclaimer. Applicants reserve the right to pursue claims directed to the subject matter of claims 45, 50 and 52-67 in a continuing application.

**B. Summary of the Interview**

Applicant thanks the Examiner for extending them the courtesy of an interview on April 11, 2006. Examiner Gollamudi, Dr. Morten Weidner, Kim Wagner and Todd Spalding participated in the interview.

The participants discussed the state of the prior art, and Dr. Weidner explained that none of the cited references suggested that Shea butter fractions would have an anti-inflammatory effect when orally administered. Dr. Weidner described many physiological factors that made the effects of Shea butter fractions, when orally administered, unpredictable. He further explained that the pharmacological effects of butyrospermol described in GB 932,662 were not anti-inflammatory effects.

Examiner Gollamudi asked for a written reply to the final Office Action and stated that she would further consider the merits of the pending claims.

**C. Definiteness Requirement of 35 U.S.C. § 112**

The Office alleged that claim 45 fails to meet the requirement of 35 U.S.C. § 112 that claims particularly point out and distinctly claim the invention. In particular, the Office stated that the requirement for compositions to be “encapsulated” is unclear. Applicants respectfully disagree with the rejection. Nevertheless, the cancellation of claim 45 has rendered the rejection moot. Withdrawal of the rejections, therefore, is appropriate.

**D. Compositions of Claims 52-67**

The Office alleged that various references either anticipate or render obvious the compositions of claims 52-67 35 U.S.C. §§ 102-103. Applicants respectfully disagree with the rejection. Nevertheless, the cancellation of claims 52-67 has rendered the rejections moot. Withdrawal of the rejections, therefore, is appropriate.

**E. Claims 41, 45-48 and 50-51 Are Patentable Over the Cited Art**

The Office asserted that claims 41, 45-48 and 50-51 are unpatentable under 35 U.S.C. § 103(a) for being obvious over WO 99/63031 (“Alander”) in view of GB 932,662. Applicants traverse the rejection.

1. Alander

According to the Office, Alander “discloses the anti-inflammatory properties of the [triterpene] fractions” of shea butter, but “does not specify the use of an oral pharmaceutical composition.” The former statement is inaccurate.

With regard to the alleged disclosure of anti-inflammatory properties, Alander describes a biological *in vitro* experiment wherein human epidermal keratinocytes were stimulated with croton oil, after which the secretion of cytokines IL-8 and IL-1 $\alpha$  was measured. Several fractionated plant oils, including Shea butter, were tested for their effect on the cytokine secretion.

In contrast to other substances tested, fractionated Shea butter increased the secretion of IL-8. In that regard, Alander stated that “a synergistic response was detected with the combination of croton oil and Shea butter fraction: IL-8 release increased significantly when NHEK were treated by Shea butter fraction at C3 and C4.” Thus, the observed effect of Shea

butter on IL-8 must be characterized as *pro-inflammatory*; IL-8 is a powerful chemokine capable of attracting inflammatory cells to a site of inflammation.

While it is acknowledged that the Shea butter fraction had a modest inhibitory effect on IL-1 $\alpha$ , the skilled artisan studying Alander's test results still would seriously question whether Shea butter has any anti-inflammatory effect.

Moreover, because Alander's test was performed in dermal keratinocytes, which form the outer layer of the skin, the data are only relevant to topical dermatological application. No systemic anti-inflammatory effects or effects relevant to muscle or joint inflammation were observed. This is perfectly consistent with the fact, acknowledged by the Office, that Alander does not even suggest oral administration of fractionated Shea butter.

Thus, the skilled artisan would learn from Alander that fractionated Shea butter arguably has a modest anti-inflammatory effect when *topically* administered, but would learn nothing about the effect of fractionated Shea butter when orally administered.

## 2. GB 932,662

According to the Office, GB 932,662 discloses a therapeutic composition containing butyrospermol from *Butyrospermum parkii* and the oral administration of such a composition. However, the document does not teach or suggest an anti-inflammatory effect from the oral administration of butyrospermol.

When considering GB 932,662, it is important to remember that cortisone, which primarily is active in a hydroxy-steroid form (hydrocortisone, or cortisol), has a broad spectrum of physiological effects. Some of these effects are described in Nussey & Whitehead: "Endocrinology: An Integrated Approach," Bios Scientific Publishers, ISBN: 1859962521, pp. 126-127 (copy attached), a recognized textbook that is available online at the homepage of the US National Library of Medicine:

- Cortisone, like the thyroid hormone T<sub>3</sub>, has potent metabolic effects on many tissues. These effects are essentially anabolic in the liver and catabolic in muscle and fat. The overall metabolic effect is to increase blood glucose concentrations.

- Cortisone has diverse effects on the cardiovascular system. It plays an essential role in sustaining normal blood pressure by maintaining normal myocardial function and the responsiveness of arterioles to catecholamines and angiotensin II.
- Cortisone has diverse effects on the CNS. It can alter the excitability of neurons, induce neuronal death (particularly in the hippocampus), and affect the mood and behavior of individuals.
- Cortisone regulates various kidney functions. It increases glomerular filtration rate by increasing glomerular blood flow, and increases phosphate excretion by decreasing its reabsorption in the proximal tubules. In excess, cortisone has aldosterone-like effects in the kidney causing salt and water retention.
- Cortisone impacts fetal development. It facilitates fetal maturation of the central nervous system, retina, skin, gastrointestinal tract and lungs. It also is particularly important in the synthesis of alveolar surfactant, which occurs during the last weeks of gestation.

Thus, reducing inflammation is only one of many effects of cortisone.

GB 932,662 describes three pharmacological effects of cortisone, each of which relates to metabolic and blood glucose enhancing effects that are unrelated to inflammation:

*Hormonal activity*

GB 932,662 experimentally shows that rats orally administered butyrospermol survive cooling (+3°C) after suprarenalectomy better than untreated control rats. It concludes that butyrospermol possesses a cortisone-like effect. The cortisone-like effect, however, was not an anti-inflammatory effect. Cortisone performs a number of functions in the body and in that particular experiment, cortisone was responsible for releasing glucose to the cooled tissues, thereby keeping a base level of metabolism going in the cooled tissues. The fact that butyrospermol might exert a similar effect does not mean that butyrospermol exerts *all* the effects of cortisone. GB 932,662 did not investigate inflammation, so the skilled artisan could not conclude that butyrospermol exerts the anti-inflammatory effects of cortisone.

*Cicatrizing properties*

GB 932,662 demonstrates cicatrizing effects in the cornea of rabbits. The disclosed data does not show that butyrospermol has an anti-inflammatory activity, though.

*Bacteriostatic effects*

GB 932,662 demonstrates bacteriostatic effects of butyrospermol, but such effects are not related to anti-inflammatory activity.

Thus, GB 932,662 does not disclose anti-inflammatory effects of butyrospermol after oral administration.

C. The Combination of Alander and GB 932,662

Combining Alander with GB 932,662, the Office stated that “[o]ne would have been motivated to use an oral vehicle comprising the extract with an expectation of success since first Alander teaches the extract in a cosmetic or pharmaceutical composition and GB ‘662 teaches the use of *Butyrospermum parkii* triterpene alcohol fractions may be administered using oral vehicles for systemic administration or topical vehicles for local effect.” However, the Office really failed to identify such a motivation in the art. Instead, it merely made a “hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.” *ATD Corp. v. Lydall, Inc.*, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). This is improper, as there must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. *See Ruiz v. A.B. Chance Co.*, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000); *ATD Corp.*, 48 USPQ2d at 1329; *Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc.*, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994).

In fact, the skilled artisan would not have been motivated to combine the teachings of the asserted references. As reviewed above, the art only taught that fractionated Shea butter potentially had modest anti-inflammatory activity when used *topically*. There was no teaching or suggestion that it would have such activity when *orally* administered. The mere fact that a composition can administered orally does not constitute a suggestion actually to do

so. Indeed, it is unreasonable to believe, without sufficient data or reasoning, that a composition will have the same effect when orally administered as it has when topically applied.

Additionally, it is significant that GB 932,662 had been published for more than 35 years before Alander and the present application, yet until the present time no one taught that oral administration of fractionated Shea butter should be performed to treat inflammation. GB 932,662 was available when Alander was published, yet Alander ignored the possibility for oral administration. That is because treating inflammation by orally administering fractionated Shea butter was not considered a realistic possibility until the present inventor proved as much.

Finally, the surprising results of Applicant's clinical experiments argues in favor of patentability. In a prior response dated August 12, 2002, Applicant presented data showing that orally administered Shea butter has pronounced curative effects on patients suffering from psoriasis and osteoarthritis. Moreover, as Example 4 of the present application shows, Shea butter is very safe when orally administered. It is surprising that strong therapeutic effects can be obtained from compositions having very low toxicity.

Because the cited art does not teach or suggest the invention of claims 41, 45-48 and 50-51, and because the claimed invention provides surprising therapeutic results, Applicant respectfully requests withdrawal of the obviousness rejection.

**F. Claims 42 and 44 Are Patentable Over the Cited Art**

The Office asserted that claims 42 and 44 are unpatentable under 35 U.S.C. § 103(a) for being obvious over WO 99/63031 ("Alander") in view of GB 932,662 and further in view of WO 9/22706 ("Sederma"). Applicants traverse the rejection.

Sederma does not remedy the deficiencies of Alander and GB 932,662, discussed above. According to the Office, Sederma "teaches a cosmetic or dermopharmaceutical composition containing plant extract of *Butyrospermum parkii* for treating dryness, dermatitis, eczema, sunburns and burns." However, the reference does not teach orally administering a *Butyrospermum parkii* extract for treating those conditions. Thus, the

combined references still lack any teaching or suggestion that fractionated Shea butter would have anti-inflammatory activity when orally administered. Again, the mere fact that a composition can administered orally does not constitute a suggestion actually to do so. It is unreasonable to believe, without sufficient data or reasoning, that a composition will have the same effect when orally administered as it has when topically applied.

**G. Claims 42-43 Are Patentable Over the Cited Art**

The Office asserted that claims 42-43 are unpatentable under 35 U.S.C. § 103(a) for being obvious over WO 99/63031 (“Alander”) in view of GB 932,662 and further in view of Kweifo-Okai et al., Res. Comm. Mol. Pathol. Pharm., 85(1): 45-55 (1994) (“Kweifo-Okai”). Applicants traverse the rejection.

Kweifo-Okai does not remedy the deficiencies of Alander and GB 932,662, discussed above. According to the Office, Kweifo-Okai “teaches triterpenes including alpha amyrin have an antiarthritic effect.” However, the reference does not teach orally administering alpha amyrin or any other triterpene to obtain an anti-arthritis effect. Thus, the combined references still lack any teaching or suggestion that fractionated Shea butter would have anti-inflammatory activity when orally administered. Again, the mere fact that a composition can administered orally does not constitute a suggestion actually to do so. It is unreasonable to believe, without sufficient data or reasoning, that a composition will have the same effect when orally administered as it has when topically applied.

**H. Claims 49 and 55 Are Patentable Over the Cited Art**

The Office asserted that claims 49 and 55 are unpatentable under 35 U.S.C. § 103(a) for being obvious over WO 99/63031 (“Alander”) in view of GB 932,662 and further in view of SU 1181171. Applicants traverse the rejection.

SU 1181171 does not remedy the deficiencies of Alander and GB 932,662, discussed above. According to the Office, SU 1181171 “teaches the anti-inflammatory properties of the marigold plant and its extract.” The reference has no relation to fractionated Shea butter, so the combined references still lack any teaching or suggestion that fractionated Shea butter would have anti-inflammatory activity when orally administered.

Additionally, the Office did not identify a sufficient motivation or suggestion to combine SU 1181171 with the other references. The mere fact that two compounds both have anti-inflammatory activity is not motivation to jointly administer the two compounds. It is not enough that the compounds could be combined. In the absence of a specific motivation or suggestion, this rejection also appears to be based on a “hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.” *ATD Corp.*, 48 USPQ2d at 1329.

### I. Concluding Remarks

Applicant believes that this application is now in condition for allowance, and requests favorable reconsideration of it. If the Examiner believes that an interview would advance prosecution of the application, she is invited to contact the undersigned attorney by telephone.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

By 

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# Endocrinology

*An Integrated Approach*

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# Actions of glucocorticoids and clinical features of Cushing's syndrome

Cortisol, like the thyroid hormone  $T_3$ , has potent metabolic effects on many tissues (Box 4.9). These are essentially anabolic in the liver and catabolic in muscle and fat; the overall effect is to increase blood glucose concentrations. Thus, like growth hormone, epinephrine and glucagon, cortisol is also considered diabetogenic. It does this by opposing the action of insulin in peripheral tissues (decreasing glucose uptake via GLUT4 receptors) and increasing glucose production and release from the liver. The latter is accomplished through gluconeogenesis using amino acids (from the catabolic actions on muscle) as the primary carbon source (Box 4.9). Thus, *Clinical Cases 4.1* and *4.2* had thin arms and legs caused by the catabolic actions of excess glucocorticoids on peripheral muscle. Patients with Cushing's syndrome tend to have a particular weakness of the muscles around the hips and shoulders, termed a proximal myopathy.

Although cortisol has some minor lipolytic activity, this effect is overshadowed in a patient with Cushing's syndrome by the increased insulin secretion in response to the diabetogenic actions of cortisol. Insulin has a strong lipogenic action (see Box 2.8) and, thus, the excess glucocorticoids seen in *Clinical Cases 4.1* and *4.2* increased fat deposition. The reason for the centripetal distribution of fat is not fully explained but probably results from metabolic differences between adipocytes in the omentum and those situated in subcutaneous tissues.

Bruising, scarring and purple striae around the abdomen are other classical signs of Cushing's syndrome (Box 4.10). Cortisol inhibits fibroblast proliferation and also the formation of interstitial materials such as collagen. Excess glucocorticoids result in a thinning of the skin and the loss of connective tissue support of capillaries. This makes them more susceptible to injury and leads to bruising. Bones are also affected by excess glucocorticoids. Cortisol decreases osteoblast function and decreases new bone formation; osteoclast numbers increase and measures of their activity increase. Furthermore, glucocorticoids decrease gut calcium absorption and decrease renal calcium reabsorption, thus adversely affecting calcium balance. Overall excess glucocorticoids cause osteoporosis.

Glucocorticoids have other diverse actions including those on the cardiovascular system, central nervous system, kidney and the fetus. In the cardiovascular system, it is required for sustaining normal blood pressure by maintaining normal myocardial function and the responsiveness of arterioles to catecholamines and angiotensin II. In the CNS, cortisol can alter the excitability of neurons, induce neuronal death (particularly in the hippocampus) and can affect the mood and behavior of individuals. Depression may be a feature of glucocorticoid therapy.

Imaging the adrenal gland

Treatment of Cushing's syndrome

Nelson's syndrome

Excess adrenal androgens - congenital adrenal hyperplasia (CAH)

Deficiency of adrenocortical secretions - Addison's disease

Aldosterone and the control of salt and water balance

Transport and metabolism of adrenocortical steroids

Selective mineralocorticoid excess and deficiency

The adrenal medulla and pheochromocytoma

Catecholamine synthesis and secretion

Diagnosis and treatment of pheochromocytomas

Clinical case questions

**Boxes**

Box 4.9. Diagram

showing the major actions...

Box 4.10. Clinical

features of Cushing's syndrome

Box 4.11. Cortisol

and the aldosterone receptor...

Box 4.12. Major

effects of glucocorticoids on...

Furthermore, depressed patients may show increased cortisol secretion with alteration in the circadian rhythm of cortisol secretion.

In the kidney, cortisol increases glomerular filtration rate by increasing glomerular blood flow and increases phosphate excretion by decreasing its reabsorption in the proximal tubules. In excess, cortisol has aldosterone-like effects in the kidney causing salt and water retention. This is because the capacity of  $11\beta$ -hydroxysteroid dehydrogenase type 1 enzyme that converts active cortisol to inactive cortisone in the kidney tubule is overwhelmed. Cortisol is then available to interact with the aldosterone receptor for which it has equal affinity (Box 4.11). This may be a factor in the hypertension seen in patients with Cushing's syndrome.

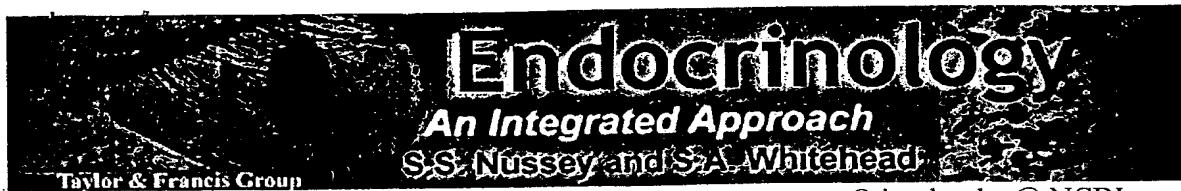
Cortisol also facilitates fetal maturation of the central nervous system, retina, skin, gastrointestinal tract and lungs. It is particularly important in the synthesis of alveolar surfactant which occurs during the last weeks of gestation. Babies born prematurely may suffer respiratory distress syndrome and mothers with pre-term labor may be treated with glucocorticoids to stimulate fetal synthesis of surfactant.

One of the most important actions of glucocorticoids is on inflammatory and immune responses (Box 4.12) and it is these actions which led to the development of a multi-million dollar pharmaceutical industry in synthetic glucocorticoid preparations. Inflammation (increased capillary permeability, attraction of leukocytes etc.) results from injury and these effects are mediated by several factors the production of which is inhibited by cortisol.

Some of these factors are synthesized from arachidonic acid and cortisol inhibits the synthesis and release of arachidonic acid by inducing lipocortin which inhibits phospholipase A<sub>2</sub>. This enzyme releases arachidonic acid from phosphatidyl choline and, thus, the availability of arachidonic acid for the synthesis of inflammatory mediators is reduced. In addition glucocorticoids stabilize lysosomes, preventing the release of proteolytic enzymes. They inhibit the proliferation of mast cells, production of cytokines and also the recruitment of leukocytes to the site of infection or trauma. They also affect the numbers and functions of circulating neutrophils, eosinophils and fibroblasts. In addition, glucocorticoids reduce the number of circulating thymus derived lymphocytes (T-cells) and as a result the recruitment of B lymphocytes. The net result is to reduce both cellular and humoral immunity.  

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## Endocrinology

An Integrated Approach

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